# Nervous Complications of Exanthem Subitum

PHILLIP E. ROTHMAN, *M.D.*, and
MORRIS J. NAIDITCH, *M.D.*, Beverly Hills

• **For many years it was generally believed that all convulsions associated with exanthem subitum were febrile in origin. More recently several investigators have suggested that the causative agent of this disease has a selective action on brain tissue aside from the effect of high temperature. In support of this concept are a variety of neurological manifestations sometimes observed during the course of exanthem subitum. These include prolonged and repeated convulsions, hemiparesis, headache, vomiting, bulging fontanelle, vertigo, cervical rigidity, extreme irritability and a reversal of the time of sleep. Abnormalities in the spinal fluid have been reported on a few occasions.**

**By chance the authors observed a case of exanthem subitum that began with a prolonged and severe afebrile convulsion and transient left hemiparesis. Serial electroencephalograms showed a focal lesion with suppression and slowing in the right parietal area. Behavior disorders of brief duration were noted. This case is interpreted as additional evidence of the presence of an encephalitic process.**

**The nature of the cerebral lesion remains unknown. The remote possibility of disturbed behavior in later life deserves consideration.**

In 1927 Faber and Dickey[7] reviewed the symptomatology of exanthem subitum (roseola infantum) and listed some of the neurological manifestations. Included in the list were drowsiness during the day and wakefulness and irritability at night, headache in older children and head shaking in young infants, excessive crying, a bulging fontanelle, extreme irritability, vomiting and convulsions. Eight of the 570 patients analyzed in their report had generalized convulsions. One child had three successive convulsive seizures and was unconscious for more than four hours.

Berenberg, Wright and Janeway[4] in an analysis of 181 cases noted several patients who were unusually drowsy after one or a series of convulsions. They stated that the seizures were usually generalized, tonic or clonic in character, of short duration and presumably febrile in origin. Two patients had postconvulsive hemiplegia, which cleared in two and five days respectively. It was their impression that the hemiplegia was almost certainly due to the preceding convulsions rather than to roseola *per se*. Lumbar puncture was done often and no significant alterations in the spinal fluid were observed. (In one case lymphocytes numbered 25 per cu. mm.)

Scattered instances of affection of the nervous system in exanthem subitum have appeared in the literature. Wallfield[23] described the case of a 12-year-old boy with encephalitic manifestations at the onset of the illness. During the first two days vomiting, fever, headache, vertigo and stiffness of the neck occurred, and there was a questionable convulsive seizure. The characteristic drop in temperature, rash, leukopenia and rapid recovery followed. The spinal fluid was normal.

Rosenblum[22] reported the case of a 19-month-old girl whose illness began with rectal temperature of 103°F. and a generalized convulsion of ten minutes' duration. Three additional convulsions occurred during the first day of the illness and two of them lasted about three hours. Just before the appearance of the rash, left hemiplegia was noted. The weakness gradually subsided and cleared entirely over a period of ten weeks.

Posson[20] reported three cases of exanthem subitum, each with hemiplegia following prolonged convulsions. The duration and recurrences of the convulsions were not consistent with simple febrile origin. The hemiplegia cleared promptly in one child, but residual weakness persisted in the others. Posson suggested that the causative agent had a selective action on brain tissue aside from the effect of high temperatures.

Holliday[13] reported five cases of pre-eruptive roseola encephalitis. Signs and symptoms referable to the central nervous system antedated the eruption in all cases—by as much as seven days in one instance. One patient had coma and athetosis. Two patients had cervical rigidity. Three had bulging of the anterior fontanelle. The cerebrospinal fluid was under increased pressure in three patients and in two patients the cell count was increased—to 23 cells per cu. mm. in one case and 40 in the other. All patients promptly recovered. In one patient (who had family history of epilepsy) petit mal seizures developed one and one-half years later.

Friedman, Golomb and Aronson[11] reported the case of a nine-months-old male infant in whom generalized convulsions with loss of consciousness

Presented before the Section on Pediatrics at the 86th Annual Session of the California Medical Association, Los Angeles, April 28 to May 1, 1957.

From the Department of Pediatrics, Cedars of Lebanon Hospital, Los Angeles 29, California.

developed about one day after the onset of fever. The convulsion was associated with a temperature of 104°F. Later, right sided convulsions developed and continued intermittently for four hours. Sedatives were administered. Consciousness was regained after 17 hours. On the third day of the illness, right hemiplegia was noted. The following day a rash typical of roseola appeared and the temperature dropped to normal. Leukopenia was present at the onset. Clear spinal fluid obtained during the febrile stage contained red blood cells, probably traumatic in origin. On the sixth day the spinal fluid contained 20 leukocytes per cu. mm., principally polymorphonuclear cells. The child was discharged from the hospital on the eighteenth day after onset of illness, in good condition but with a slight weakness of the extremities on the right side.

Windorfer[24] personally observed 117 cases of exanthem subitum over a period of four years. Convulsions occurred in 35 cases, vomiting in 39, meningism in 24 and bulging of the fontanelle in one. Spinal puncture was done in 28 cases in which meningitis was suspected. The fluid was always clear and showed increased pressure. The number of cells in the spinal fluid was definitely increased in three cases and the Pandy reaction was positive in two cases. The patients were less irritable after the withdrawal of fluid. Repeated convulsions occurred in 12 cases—all in one day in six patients and on successive days in six others. Four cases of paresis subsequent to convulsions were observed. These included a flaccid paresis of the left arm of two days' duration, a hemiparesis of the left arm and leg which regressed within 24 hours, a paresis of the right side which regressed slowly within a period of six weeks, and a hemiparesis on the left side which regressed within 24 hours associated with facial paresis which cleared within a few days.

In the records of the Massachusetts General Hospital published weekly in the *New England Journal of Medicine* (case 42121)[16] an additional case was briefly mentioned. A girl, aged 21 months, showed, at autopsy, Wilms' tumor of both kidneys, subacute glomerulonephritis and bronchopneumonia. According to the history she had roseola at seven months of age. At the termination of this illness she had convulsions of six hours' duration and subsequently the left side was paralyzed for two months. She regained full motion and power and seemed well afterward. The discussor commented on the rarity of central nervous system involvement at the end rather than at the onset of roseola. Pathologic studies of the brain were not included in the report.

Moller[19] reviewed the histories of 448 children with febrile convulsions in order to determine if any special diseases dispose the patient to this complication. Pharyngitis was associated with nearly 80 per cent of the cases and exanthem subitum was second with almost 8 per cent of the total. Twenty-nine of the children with exanthem subitum were subjected to lumbar puncture and in six cases the spinal fluid pressure was considered to be increased. The number of leukocytes in the spinal fluid did not exceed 9 per cu. mm. Subsequently, two of the children who had convulsions with exanthem subitum had repeated attacks of convulsions in connection with fever, and in one a very troublesome grand mal epilepsy developed. In the child with epilepsy there was no family history of convulsive disorders, no signs of cerebral lesions, and no abnormal electroencephalographic alterations. Moller suggested that exanthem subitum does not cause convulsions merely through fever but that a specific cerebral disturbance occurs at the same time.

Glanzmann (cited by Moller[19]) also pointed out that children with exanthem subitum seem to show signs of cerebral affection: They toss to and fro, vomit and are tender to touch; older children also complain of headache. Glanzmann believed that a serous meningitis is present in many cases in which bulging of the fontanelle occurs. He observed one case of exanthem subitum with convulsions and hemiparesis.

The following case was observed by the authors:

A white boy, aged two years and four months, was observed to be playing normally in his crib five hours before the sudden onset of a convulsion. Two days previously he had received a minor injury of the head (right frontal area) without loss of consciousness or any symptoms suggestive of concussion. His birth and development had been normal. At 4 a.m. the parents were awakened and found the child semicomatose and with convulsive movements of the left side. The father, an optometrist, noticed that the right pupil was larger than the left.

When the patient was examined by a pediatrician (M.N.) 45 minutes later, the skin was cool to palpation; the infant was stuporous; the head and eyes were turned to the left; the right pupil was larger than the left; repeated slow jerking movements of the left side of the face and left arm occurred almost simultaneously and were followed immediately by similar movements of the left lower extremity. The right extremities were mildly flaccid. Sodium phenobarbital was administered, 0.12 gm. intramuscularly and 0.06 gm. intravenously, without any discernible effect on the seizure.

The child was admitted to the hospital at 5:30 a.m. and at that time the rectal temperature was 99.8°F. No antipyretics had been administered. The convulsion persisted for a total duration of 2 hours and 45 minutes. At 6:10 a.m. the temperature was 100.6°F. The first electroencephalographic tracing was recorded at 11:00 a.m. and at 1:15 p.m. the

temperature was 103°F. Toward evening the sensorium partly cleared and the patient was able to follow the movement of objects with his eyes but was unable to speak. Left hemiparesis was present. There was no response to painful stimuli in the left arm and only slight withdrawal from stimuli in the left leg. All deep reflexes were decidedly diminished and difficult to evoke. The right toe sign was positive and the left equivocal. No hemorrhages or signs of pressure were apparent on examination of the fundi of the eyes. The spinal fluid obtained shortly after admission was clear; the pressure was 120 mm. of water; it contained 4 cells per cu. mm.; the protein content was 11.0 mg. per 100 cc. and the sugar content 100 mg. per 100 cc. No organisms grew on a culture. No abnormalities were detected in x-ray films of the skull. Leukocytes numbered 13,700 per cu. mm. of blood—80 per cent polymorphonuclear cells. The number of erythrocytes and the hemoglobin value were within normal limits. No alterations in the urine were present. The initial impressions included subdural hematoma, neoplasm and acquired infantile hemiplegia, so-called Marie-Strumpell encephalitis.

The following day the patient was stuporous and unable to speak. The weakness of the left side persisted. The pupils became equal in size. The rectal temperature rose to 104.2°F. The leukocyte count decreased to 3,400 with 77 per cent polymorphonuclear cells. On the third day the patient appeared mentally clearer. The presence of suboccipital adenopathy was noted for the first time. On the fourth day the temperature fell abruptly to 100°F. Leukocytes numbered 2,400 per cu. mm., with 32 per cent polymorphonuclear cells. A morbilliform rash appeared. A diagnosis of exanthem subitum seemed justifiable. The patient was greatly improved and was able to say a few words. Only a facial weakness persisted. Two weeks later there was no evidence of any residual manifestations. A complete muscle function test was done by a trained physiotherapist and no signs of weakness were noted.

Subsequently the intelligence of the patient appeared normal but for many months aggressive hyperactivity and increased irritability were observed. No convulsions have occurred in the four years that have elapsed since the illness.

#### COMMENTS ON THE ELECTROENCEPHALOGRAMS

Following is the report of a neurologist* on the electroencephalograms.

"The first electroencephalogram (Figure 1) on the day of admission to the hospital showed suppression and slowing on the right side. Suppression

*A. A. Marinacci, M.D.

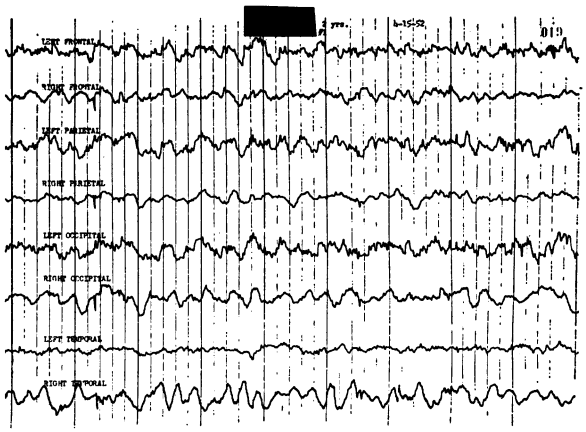

Figure 1.—Electroencephalogram of April 15, 1952 shows suppression in the right parietal area and delta activity in the parietal-temporal area denoting a focus on the right parietal-temporal area.

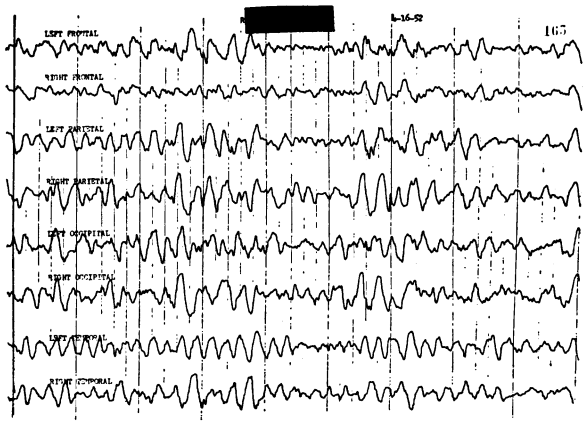

Figure 2.—Electroencephalogram of April 16, 1952 shows diffuse slowing with no focal abnormality. The focus present in Figure 1 has disappeared.

and slowing of this pattern are not pathognomonic of any disease entity, but have been found in lateral subdural hematoma, lateral cerebral abscess, focal encephalitis, unilateral cerebral thrombosis, brain tumor and focal cerebral contusion. This activity can be consistent with cerebral ischemia due to vascular occlusion. The tracing is similar to that of an adult suffering with a stroke. However, in adults, more alpha activity is present from the normal side of the brain. The abnormality on the right side cannot be distinguished from local infection.

"The generalized slowing in Figure 2 (second day of illness) is similar to that found in measles encephalitis. This slowing can also be found as the result of febrile alteration. However, in this case, when the temperature returned to normal the slowing persisted, denoting that the variation was due to physiological change and not to elevated temperature.

"The slightly increased slowing in the right parietal area in Figure 3 (27 days after onset) denotes that this area was more affected than the left and

requires a somewhat longer time to return to normal, a fact which is obvious, clinically, in this case.

"To sum up, although the first brain wave showed a definite focal variation on the right side, which may have indicated a lesion requiring surgical intervention, clinical judgment superseded the electroencephalographic findings and surgical procedures were postponed. Subsequently the electroencephalograms were of value in showing a resolution of the focus (Figure 4). These electroencephalograms also emphasize the point that the electroencephalographic findings do not differentiate between true structural changes and reversible physiological changes. Certainly in this case the changes were reversible, similar to those of a reversible physiological block seen in nerve lesions."

It seems certain that convulsions and meningoencephalitic symptoms, not febrile in origin, occasionally occur in cases of exanthem subitum. The often repeated statement that exanthem subitum has no important complications or sequels is based, chiefly, on failure to differentiate febrile convulsions from seizures due to organic lesions.

An accurate diagnosis of febrile convulsion is usually possible if one adheres to the criteria established by Bridge[5] and by Livingston.[15] The following characteristics are generally accepted. A simple febrile convulsion is a generalized seizure of short duration (about 1 to 15 minutes). It occurs soon after the onset of fever but may occasionally be delayed six to ten hours. The fever may be as low as 101°F. but is usually 103°F. or higher; and the more rapidly the body temperature is raised, the more frequently do convulsions develop. Localized features and neurological abnormalities are absent except for the occasional presence of hyperactive reflexes. Recurrent convulsions are infrequent and usually take place within two to four hours after the initial seizure and not later than 12 to 18 hours. The blood sugar, serum calcium and phosphorus determinations are within normal limits. The seizures are most common during the first three years of life and very rare after the sixth year. To this description may be added the observations that febrile convulsions appear to show excellent response to barbiturates and that the interseizure electrocardiogram is normal.

No studies have been recorded of the anatomic alterations associated with the nervous manifestations of exanthem subitum. Speculation concerning the nature of this complication is possible by analogy with the cerebral disturbances of other acute infectious diseases. The cerebral complications that follow measles, mumps, chickenpox, smallpox and injections with cowpox or rabies vaccine are alike in that the myelin is destroyed in minute perivascular or subpial foci, the axis cylinders are damaged to a much less degree and necrosis of interstitial tissue

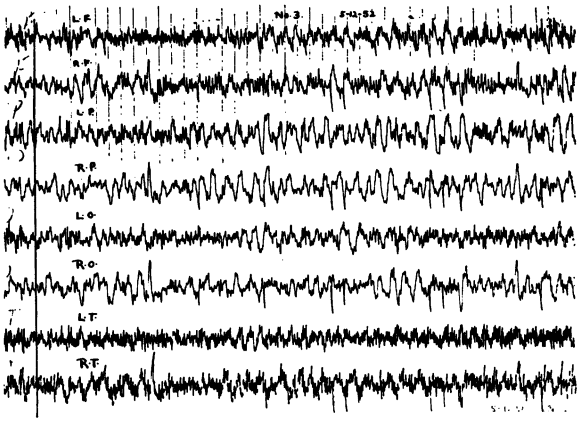


Figure 3.—Electroencephalogram of May 12, 1952 shows a considerable amount of muscle activity in the bifrontal and bitemporal areas. However, the cortical activity remained about the same as in Figure 2.

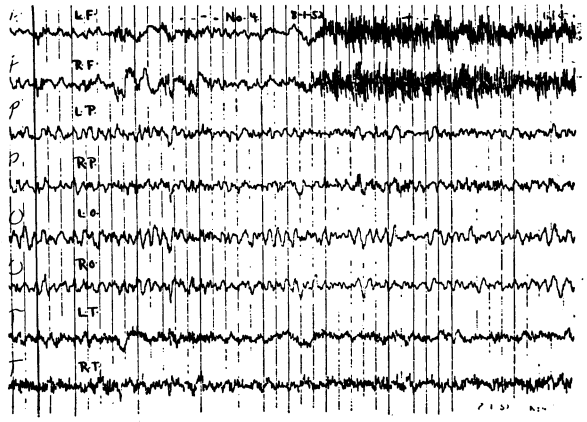


Figure 4.—Electroencephalogram of Aug. 1, 1952 shows again muscle activity in the bifrontal and bitemporal areas. However, the cerebral activity is within normal limits.

does not occur (Adams and Weinstein[1]). Hemorrhages and vascular lesions have been described[21] and Ford[8] expressed belief that vascular occlusions are probably responsible for persistent focal signs such as hemiplegias. In seven instances of acquired hemiplegia following acute infectious diseases and in two instances in apparently healthy children (Marie-Strumpell encephalitis) Ford and Schaffer[9] found evidence of some type of local vascular accident at operation or at autopsy.

Rarely has an organism been isolated from the cerebrospinal fluid or brain in cases of infectious diseases with encephalitic complications. The fact that monoplegia and hemiplegia constitute the only residual neurological manifestations of exanthem subitum is unique and suggests a thrombosis, hemorrhage or simple vasoconstriction of a cerebral artery.

The supposition that the hemiplegia associated with exanthem subitum is due to the convulsions

*per se* has been generally accepted. Little is known concerning the transient disturbances designated as postconvulsive phenomena.[10] They consist of general symptoms such as weakness, headaches, restlessness, irritability, abnormal behavior, stupor, coma, mental confusion and local symptoms such as hemianopia, various types of aphasias and palsies (Todd's paralysis). These phenomena may persist for minutes, hours or days; rarely are they permanent. They have been attributed to acute cell alterations secondary to vasoconstrictions. That such constrictions may cause focal ischemia has been proved by Echlin's[6] experiments but, as emphasized by other investigators, their culpability in a particular instance is difficult to adduce. More recent studies lend support to the view that postconvulsive phenomena may be due to vascular lesions, probably thrombotic in nature and perhaps more often venous rather than arterial. Mitchell[18] described two cases of convulsions with acute infantile hemiplegia and features pointing to intracranial venous thrombosis as a cause.

In the absence of any pathologic studies of the brain in exanthem subitum, one may tentatively conclude that the nervous symptoms described by Faber and Dickey[7] and the prolonged convulsions and hemiplegias described by other observers represent one or a combination of the following disorders: Nonspecific febrile alterations, acute disseminated or focal encephalomyelitis, general and focal vascular lesions.

Some help in the differential diagnosis of these disorders may be obtained by the interpretation of serial electroencephalographic changes in conjunction with the history and clinical findings. That fever itself without convulsions or evidence of a cerebral infection may produce electroencephalographic abnormalities has been emphasized by several observers. The changes usually consist of slow high voltage waves. Livingston noted that these abnormalities persisted in a few cases for at least three days after the patients became afebrile. Lennox and coworkers[14] expressed belief that slow waves which outlast the fever probably indicate brain injury and that the duration of slowing is related to the severity of the damage. They said that the return of the tracing to normal is not necessarily indicative of the reversibility of cellular damage but rather of the lack of influence of damaged cells on the electrical activity of the remaining normal neurones.

Baird and Garfunkel[3] recorded tracings in 12 children between 3 and 6 years of age before, during and after the intravenous injection of typhoid vaccine. The tracings of all the subjects were interpreted as normal before the injection of vaccine. During the artificially produced hyperthermia the most pronounced changes usually occurred during the rise in temperature and consisted of high voltage slow waves, spike and wave formations and an increase in delta activity. Electroencephalograms always returned to normal within three days and usually within 24 hours. The alterations were the same, irrespective of whether or not there was a previous history of convulsions. The need for caution in the interpretation of abnormal tracings during a febrile illness as indicative of disease of the central nervous system was emphasized.

Although febrile alterations of the central nervous system undoubtedly occur in exanthem subitum, the development of convulsions before the onset of fever in the case herein reported is particularly significant. This chance observation plus the associated hemiparesis and electroencephalographic disturbances provide evidence of the presence of a focal organic cerebral lesion directly related to the actual infection. Some additional help in future investigations of the nature of this lesion may possibly be obtained by determinations of spinal fluid transaminase activity. Green and co-workers[12] recently demonstrated significant elevations in the activity of this enzyme in patients with cerebral infarctions.

## COMMENT

The significance of mild and supposedly transient brain involvement associated with the acute infectious diseases has been the subject of considerable discussion. It is recognized that encephalomyelitis complicating measles may be so mild as to go undetected at the time of the acute exanthem, only to become manifest years later when pronounced abnormalities in behavioral patterns appear (Adams and Weinstein[1]). It has also been emphasized that abnormalities in mental functioning may occur in children who recover from encephalitis and that such disturbances may not be apparent in a quantitative appraisal of intelligence in terms of mental age or intelligence quotient. Meyer and Byers[17] directed attention to a change in the belief that disturbed behavior is necessarily produced by the action of the disease on the cerebrum to the concept that it ". . . is the result of the impact of environmental demands upon cerebral function qualitatively altered by disease."

In view of these observations it is not easy to accept the almost universal belief that exanthem subitum is a benign disease. It would, however, be extremely difficult to relate delayed behavioral abnormalities to this disease unless overwhelming statistical evidence confirms what must at present be considered a very remote possibility. The transient changes in behavior in the patient described herein led us to the same conclusion as that stated by Applebaum[2] in respect to measles encephalitis, namely, "We are not, however, certain that the deviations in behavior are directly due to encephalitis, for some of them could be explained perhaps

equally well on the basis of parental attitudes, such as maternal overprotection after an illness or other environmental influences."

436 North Roxbury Drive, Beverly Hills (Rothman).

**REFERENCES**

1. Adams, R. D., and Weinstein, L.: Clinical and pathological aspects of encephalitis, New Eng. J. Med., 239:865-876, 1948.

2. Appelbaum, E., Dolgopol, V. B., and Dolgin, J.: Measles encephalitis, Amer. J. Dis. Child., 77:25-48, 1949.

3. Baird, H. W., and Garfunkel, J. M.: Electroencephalographic changes in children with artificially induced hyperthermia, J. Ped., 48:28-33, 1956.

4. Berenberg, W., Wright, S., and Janeway, C. A.: Roseola infantum (exanthem subitum), New Eng. J. Med., 241: 253-259, 1949.

5. Bridge, E. M.: Epilepsy and Convulsive Disorders in Children; First Edition, p. 258, McGraw-Hill Book Co., Inc., New York, 1949.

6. Echlin, F. A.: Vasospasm and focal cerebral ischemia, Arch. Neurol. & Psychiat., 47:77-96, 1942.

7. Faber, H. K., and Dickey, L. B.: The symptomatology of exanthem subitum, Arch. of Pediat., 44:491-496, 1927.

8. Ford, F. R.: The nervous complications of measles, Bull. Johns Hopkins Hosp., 43:140-184, 1928.

9. Ford, F. R., and Schaffer, A. M.: The etiology of infantile acquired hemiplegia, Arch. Neurol. & Psychiat., 18:323-347, 1927.

10. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence; Third Edition, p. 1033, Charles C. Thomas, Springfield, Ill., 1952.

11. Friedman, J. H., Golomb, S., and Aronson, L.: Hemiplegia associated with roseola infantum (exanthem subitum), N. Y. State J. Med., 50:1749-1750, 1950.

12. Green, J. B., O'Doherty, D. S., Oldewurtel, H. A., and Forster, F. M.: Cerebrospinal fluid transaminase concentrations in clinical cerebral infarctions, New Eng. J. Med., 256: 220-221, 1957.

13. Holliday, P. B.: Preeruptive neurological complications of the common contagious diseases—rubella, rubeola, roseola, and varicella, J. Pediat., 36:185-198, 1950.

14. Lennox, M. A., Sibley, W. A., and Zimmerman, H. M.: Fever and febrile convulsions in kittens, J. Pediat., 45:179-190, 1954.

15. Livingston, S.: The Diagnosis and Treatment of Convulsive Disorders in Children; First Edition, p. 76, Charles C. Thomas, Springfield, Ill., 1954.

16. Mass. Gen. Hosp. Case 42121, New Eng. J. Med., 254:572-575, 1956.

17. Meyer, E., and Byers, R. K.: Measles encephalitis, Amer. J. Dis. Child., 84:543-579, 1952.

18. Mitchell, R. G.: Venous thrombosis in acute infantile hemiplegia, Arch. of Dis. Child., 27:95-104, 1952.

19. Moller, K. L.: Exanthema subitum and febrile convulsions, Acta Paediatrica, 45:534-540, 1956.

20. Posson, D. D.: Exanthem subitum (roseola infantum) complicated by prolonged convulsions and hemiplegia, J. Pediat, 35:235-236, 1949.

21. Putnam, T. J.: Newer conceptions of postinfectious and related forms of encephalitis, Bull. N. Y. Acad. Med., 17:337-347, 1951.

22. Rosenblum, J.: Roseola infantum (exanthem subitum) complicated by hemiplegia, Am. J. Dis. Child., 69:234-236, 1945.

23. Wallfield, M. J.: Exanthem subitum with encephalitic onset, J. Pediat., 5:300, 1934.

24. Windorfer, A.: Fever persisting for three days and followed by exanthem in infants: Exanthem subitum, Deutsche Med. Wchnschr., 79:1209-1214, 1954; Internat. Med. Digest, 65:363-365, 1954.